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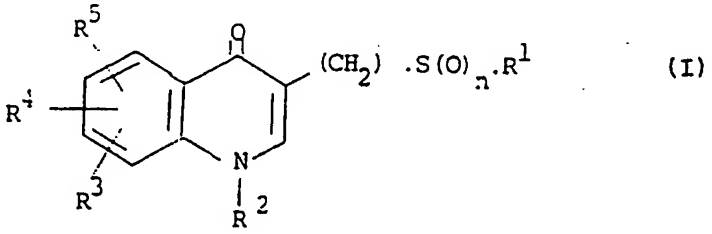

(I)

(57) Abstract

Compounds of formula (I), in which R^1 is lower alkyl; R^2 is lower alkyl; R^3 is halogenated lower alkoxy, halogenated lower alkylthio, halogenated lower alkylsulphinyl or halogenated lower alkylsulphonyl; R^4 and R^5, which may be the same or different, are hydrogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulphinyl, lower alkylsulphonyl, halo, halogenated lower alkyl, halogenated lower alkoxy, halogenated lower alkylthio, halogenated lower alkylsulphinyl, halogenated lower alkylsulphonyl, cyano, phenyl or phenyl substituted by 1 to 3, especially 1 or 2, groups selected from lower alkyl, lower alkoxy, halo or halogenated lower alkyl; m is 0 or 1; and n is 0, 1 or 2, have antihypertensive activity. Processes for preparing compounds of formula (I) and pharmaceutical compositions containing them are described.

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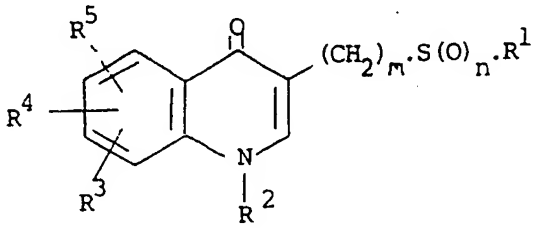
THERAPEUTIC AGENTS

This invention relates to novel quinolones having therapeutic activity useful in treating cardiovascular diseases, therapeutic compositions containing the novel quinolones and to processes for preparing the novel quinolones.

The present invention provides quinolones of formula I



I

in which R^1 is lower alkyl; R^2 is lower alkyl; R^3 is halogenated lower alkoxy, halogenated lower alkylthio, halogenated lower alkylsulphinyl or halogenated lower alkylsulphonyl; R^4 and R^5, which may be the same or different, are hydrogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulphinyl, lower alkylsulphonyl, halo, halogenated lower alkyl, halogenated lower alkoxy, halogenated lower alkylthio, halogenated lower alkylsulphinyl, halogenated lower alkylsulphonyl, cyano, phenyl or phenyl substituted by 1 to 3, especially 1 or 2, groups selected from lower alkyl, lower alkoxy, halo or halogenated lower alkyl; m is 0 or 1; and n is 0, 1 or 2.

The term "lower" as used herein signifies a group which may be straight or branched and which has 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. Lower alkyl substituents include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and hexyl. Lower alkoxy

substituents include, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy and isobutoxy. Lower alkylthio substituents include, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio and isobutylthio.

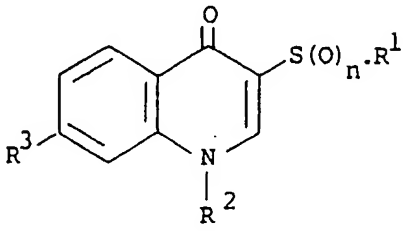
The term "halo" signifies fluoro, chloro or bromo. Halogenated substituents include fluorinated and chlorinated, preferably fluorinated, substituents such as, for example, trifluoromethyl, trifluoromethoxy, difluoromethoxy, 2,2,2-trifluoroethoxy, trifluoromethylthio, trifluoromethylsulphinyl and trifluoromethylsulphonyl.

When at least one of R^4 and R^5 is substituted phenyl the substituents may be selected from lower alkyl such as methyl or ethyl, lower alkoxy such as methoxy or ethoxy, halo such as chloro or fluoro, and halogenated lower alkyl such as trifluoromethyl.

Specific compounds of formula I are:

1-methyl-3-methylthio-7-trifluoromethoxy-4-quinolone;
1-methyl-3-methylthio-7-trifluoromethylthio-4-quinolone;
1-methyl-3-methylsulphinyl-7-trifluoromethoxy-4-quinolone, including R and S forms thereof;
1-methyl-3-methylsulphinyl-7-trifluoromethylthio-4-quinolone, including R and S forms thereof;
1-methyl-3-methylsulphonyl-7-trifluoromethoxy-4-quinolone;
1-methyl-3-methylsulphonyl-7-trifluoromethylthio-4-quinolone;
7-difluoromethoxy-1-methyl-3-methylsulphinyl-4-quinolone, including R and S forms thereof; and
1-methyl-3-methylsulphinyl-7-(2,2,2-trifluoroethoxy)-4-quinolone, including R and S forms thereof.

A preferred group of compounds of formula I may be represented by formula II



II

in which R^1, R^2, R^3 and n are as hereinbefore defined.

In preferred compounds of formula II, R^1 is alkyl having 1 to 4 carbon atoms; R^2 is alkyl having 1 to 4 carbon atoms; R^3 is fluorinated alkoxy having 1 to 4 carbon atoms, fluorinated alkylthic having 1 to 4 carbon atoms, fluorinated alkylsulphinyl having 1 to 4 carbon atoms or fluorinated alkylsulphonyl having 1 to 4 carbon atoms; and n is 0, 1 or 2.

More preferred compounds of formula II are those in which R^1 is alkyl having 1 to 4 carbon atoms; R^2 is alkyl having 1 to 4 carbon atoms; R^3 is trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy or trifluoromethylthio; and n is 0, 1 or 2.

In particularly preferred compounds of formula II, R^1 and R^2 are methyl; R^3 is trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy or trifluoromethylthio; and n is 0, 1 or 2.

Especially preferred compounds of formula II are those in which R^1 and R^2 are methyl; R^3 is trifluoromethoxy or trifluoromethylthio; and n is 0, 1 or 2, preferably 0 or 1, most preferably 0.

Certain of the compounds of formula I may form acid addition salts with certain acids. It will be

appreciated that such salts, provided they are pharmaceutically acceptable, may be used in therapy in place of the corresponding compounds of formula I. Such salts may be prepared for example by reacting the compound of formula I with a suitable acid in a conventional manner.

It will also be appreciated by those skilled in the art that certain compounds of formula I contain one or more chiral centres. Thus, compounds of formula I in which n is 1 contain a chiral centre at the sulphur atom and certain of the substituents R^1, R^2, R^3, R^4 and R^5 also contain at least one chiral centre, for example when R^1, R^2, R^4 or R^5 is sec-butyl or R^3, R^4 or R^5 is trifluoromethylsulphinyl. Such compounds may exist as two or more stereochemical isomers. When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms which may be obtained by methods known to those skilled in the art. Such methods typically include resolution via formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective derivatisation of one enantiomer by reaction with an enantiomer-specific reagent, for example enzymatic oxidation or reduction; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support or in the presence of a chiral solvent. Alternatively, it may be possible to synthesise a specific enantiomer by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or to convert one enantiomer into the other by asymmetric transformation. The present invention includes each enantiomer of compounds of formula I and mixtures thereof. When a compound of formula I contains more than one chiral

centre it may exist in diastereoisomeric forms. The diastereoisomers may be separated by methods known to those skilled in the art, for example chromatography or crystallisation. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

Certain compounds of formula I may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

The present invention also provides pharmaceutical compositions which comprise a compound of formula I as hereinbefore defined together with a pharmaceutically acceptable carrier. Specific compounds which may be incorporated into the compositions of this invention are the novel compounds disclosed above.

As used hereinafter, the term "active compound" denotes a quinolone of formula I. In therapeutic use the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention suitably contain 0.1-90% by weight of active compound. The compositions

of the invention are generally prepared in unit dosage form.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oily suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacists' art.

Tablets may be prepared by mixing the active compound with an inert diluent, such as lactose or calcium phosphate, in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. Such tablets may if desired be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly capsules, for example hard or soft gelatin capsules containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. Enteric coated compositions of the invention may be advantageous, depending on the nature of the active compound. The tablets and capsules may conveniently each contain 1-500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the compound of formula I in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such adminstration, for example suppositories with semi-synthetic glycerides or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous and oily media or sterile solutions in a suitable solvent.

Compositions for topical administration may comprise a matrix in which the active compound is dispersed so that it is held in contact with the skin in order to administer the compound of formula I transdermally. Alternatively the active compound may be dispersed in a cream or ointment base.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

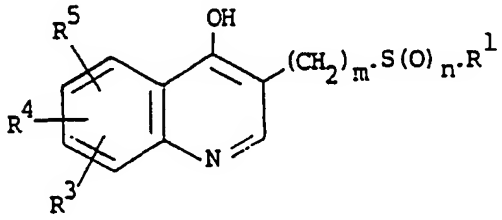
In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients, for example a ß-blocker such as propranolol, oxprenolol, atenolol, nadolol or timolol, or a diuretic such as bendrofluazide.

The therapeutic activity of compounds of formula I has been demonstrated by means of tests on standard laboratory animals. Such tests include, for example, the oral administration of the compounds to a strain of spontaneously hypertensive rat. Thus, compounds of formula I are useful for reducing blood pressure in hypertensive mammals. Whilst the precise amount of

active compound administered will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history and always lies within the sound discretion of the administering physician, a suitable dose for enteral administration to mammals, including humans, is generally within the range 0.01-25 mg/kg/day, more usually 0.2-10 mg/kg/day given in single or divided doses. For parenteral administration, a suitable dose is generally within the range 0.001-2.5 mg/kg/day, more usually 0.005-1 mg/kg/day given in single or divided doses or by continuous infusion. Oral administration is preferred.

Compounds of formula I are vasodilators with an action on both arterial and venous vascular beds. Accordingly, compounds of formula I are indicated for use in the treatment of ischaemic heart disease and heart failure in mammals, including humans. Suitable dosages are as hereinbefore stated.

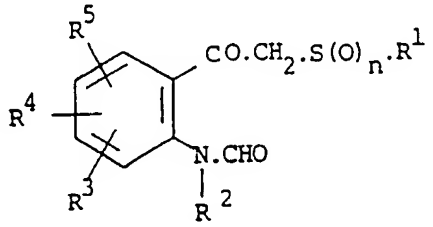
The compounds of formula I may be prepared by alkylation of a compound of formula III



III

with an alkylating agent of formula $(R^2)_2SO_4$ or an alkylating agent of formula R^2Y in which Y is a leaving group, for example halo, preferably iodo. The reaction may preferably be carried out in the presence of a base, for example potassium hydroxide.

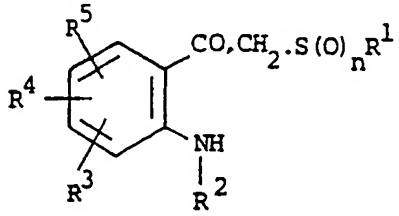
Compounds of formula I in which m is 0 may be prepared by cyclisation of a compound of formula IV



IV

The cyclisation reaction may be effected in the presence of an organic or inorganic base or by heating the compound of formula IV in a liquid inert to the conditions of the reaction.

Compounds of formula I in which m is 0 may be prepared by reaction of a compound of formula V

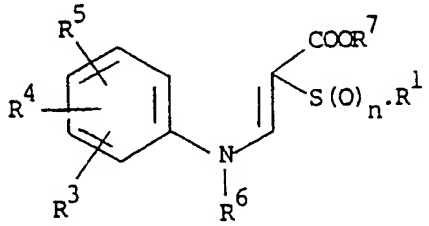


V

with a tri(lower alkyl) orthoformate, preferably trimethyl orthoformate or triethyl orthoformate. The reaction may be effected by heating in a solvent inert

to the conditions of the reaction in the presence of a base such as, for example, piperidine.

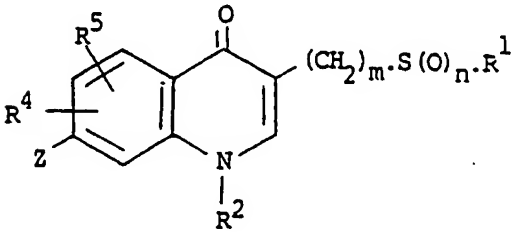
Compounds of formula I in which n is 0 or 2 and m is 0 may also be prepared by cyclisation of a corresponding acrylate of formula VI



VI

in which R^7 is lower alkyl, preferably methyl or ethyl, and R^6 is R^2. Cyclisation may be effected, for example by heating a compound of formula VI in a mixture of acetic anhydride and concentrated sulphuric acid. It will be apparent to those skilled in the art that the reaction may produce a mixture of isomers. The desired compound of formula I may be separated using methods known in the art.

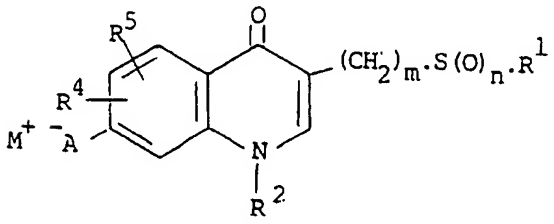
Compounds of formula I in which R^3 is halogenated lower alkoxy, halogenated lower alkylthio or halogenated lower alkylsulphonyl in the 7-position of the quinoline ring may be prepared by reaction of a compound of formula VII



VII

in which Z is fluoro, chloro or bromo, preferably fluoro, with the appropriate halogenated anion in a solvent inert to the conditions of the reaction. For example compounds of formula I in which R^3 is 7-(2,2,2-trifluoroethoxy) may be prepared from a compound of formula VII in which Z is fluoro by reaction with sodium 2,2,2-trifluoroethoxide in dioxan.

Compounds of formula I in which R^3 is halogenated lower alkoxy or halogenated lower alkylthio in the 7-position of the quinoline ring may also be prepared by reaction of a compound of formula VIII



VIII

in which A is oxygen or sulphur and M^+ is a cation such as an alkali metal cation, for example sodium, with an appropriate alkylating agent. For example compounds of formula I in which R^3 is 7-difluoromethoxy may be prepared from a compound of formula VIII in which A is oxygen and M^+ is sodium by reaction with chlorodifluoromethane.

Compounds of formula I in which R^3 is fluorinated lower alkoxy may also be prepared by reaction of a compound of formula I in which R^3 is fluorinated chloroalkoxy with a mild fluorinating agent such as potassium fluoride or silver tetrafluoroborate. For example a compound of formula I in which R^3 is trifluoromethoxy may be prepared by reaction of a

compound of formula I in which R^3 is chlorodifluoromethoxy with silver tetrafluoroborate.

Compounds of formula I in which R^3 is fluorinated chloroalkoxy or fluorinated chloroalkylthio in the 7-position of the quinoline ring may be prepared by reaction of a compound of formula VIII in which M^+ is a cation such as an alkali metal cation, for example sodium, with a fluorinated polychloroalkane. For example a compound of formula I in which R^3 is chlorodifluoromethoxy may be prepared by reaction of a compound of formula VIII in which A is oxygen and M^+ is sodium with dichlorodifluoromethane.

Compounds of formula I or formula III in which n is 1 or 2 and R^3 is halogenated alkoxy may be prepared by oxidation of a corresponding compound of formula I or formula III in which n is 0 or 1, using for example, a peroxycarboxylic acid such as 3-chloroperoxybenzoic acid as the oxidising agent.

Compounds of formula I or formula III in which n is 1 and R^3 is halogenated alkylthio may be prepared by oxidation of a corresponding compound of formula I or formula III in which n is 0, using for example, a peroxycarboxylic acid such as 3-chloroperoxybenzoic acid as the oxidising agent.

Compounds of formula I or formula III in which n is 2 and R^3 is halogenated alkylsulphinyl may be prepared by oxidation of a corresponding compound of formula I or formula III in which n is 2 and R^3 is halogenated alkylthio, using for example, a peroxycarboxylic acid such as 3-chloroperoxybenzoic acid as the oxidising agent.

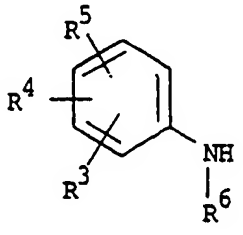
Compounds of formula I or formula III in which n is 1 or 2 and R^3 is halogenated alkylsulphonyl may be prepared by oxidation of a corresponding compound of formula I or formula III in which n is 0 or 1, using for example, a peroxycarboxylic acid such as 3-chloroperoxybenzoic acid as the oxidising agent.

Compounds of formula I or formula III in which n is 2 and R^3 is halogenated alkylsulphonyl may be prepared by oxidation of a corresponding compound of formula I or formula III in which n is 0, 1 or 2 and R^3 is halogenated alkylthio or halogenated alkylsulphinyl, using a strong oxidising agent, for example hydrogen peroxide in acetic acid.

Compounds of formula I in which n is 0 and R^3 is halogenated alkylthio may be prepared by reduction of a corresponding compound of formula I in which n is 0 or 1 and R^3 is halogenated alkylsulphinyl using, for example, triphenylphosphine as the reducing agent.

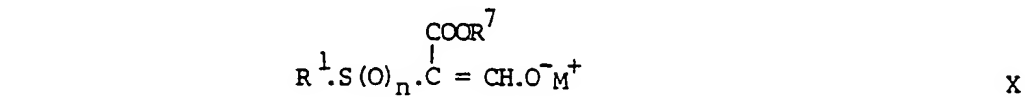
Compounds of formula III in which n is 0 or 2 and m is 0 may be prepared, for example, by cyclisation of a corresponding compound of formula VI in which R^6 is hydrogen. Cyclisation may be effected, for example by heating a compound of formula VI in a liquid inert to the conditions of the reaction such as diphenyl ether for example within the range 200-280°.

Compounds of formula VI may be prepared by reaction of a compound of formula IX



IX

in which R^6 is hydrogen or lower alkyl, with an acrylate of formula X



X

in which n is 0 or 2 and M^+ is an alkali metal cation, for example sodium.

Compounds of formula VIII may be prepared by nucleophilic substitution of a compound of formula VII for example, by reaction of a compound of formula VII in which Z is fluoro with aqueous sodium hydroxide.

Compounds of formula IV, V and VII are novel but may be prepared by methods analogous to those described in UK Patent No. 2047691, UK Patent No. 2085441 and European Patent Application No. 0317149 for the preparation of similar compounds. Some of the compounds of formulae IX and X are known but it will be apparent to those skilled in the art that novel compounds may be prepared in a similar manner to the preparation of the known compounds of said formulae.

The preferred group of compounds of formula II may be prepared using appropriate methods disclosed hereinbefore for preparing compounds of formula I.

The therapeutic activity of compounds of formula I in Table 1 has been demonstrated by the following test which involves the oral administration of the compounds to a strain of spontaneously hypertensive rat. This test was carried out in the following way:

Test

Female rats, weight range 180-240g, of the Aoki-Okamoto strain of spontaneously hypertensive rat were used. The rats in groups of four were fasted overnight before administration of the test compound. Blood pressure was determined in the following way. The rats were placed in a cabinet kept at 38°C with their tails protruding through holes in the cabinet. After 30 minutes in the cabinet blood pressure was measured using an inflatable cuff placed round the base of the tail and arterial pulsations monitored with a pneumatic pulse transducer. A pressure, greater than the expected blood pressure, was applied to the cuff, and this pressure was slowly reduced. The pressure in the cuff at which arterial pulsations reappeared was taken as the blood pressure. The rats were removed from the cabinet and each group orally dosed with a given dose of the test compound given as a solution or suspension in 0.25% aqueous carboxymethylcellulose. In addition to the pre-dose reading, blood pressure was measured at 1.5 and 5.0 hours after dosing. The degree of blood pressure reduction sufficient to achieve a significance level of $p<0.01$ compared to controls was 9% after correction for control changes at appropriate time intervals. Thus, compounds were considered to be active in this test if they produced a reduction of blood pressure after correction of 9% or greater than 9%.

Threshold antihypertensive doses of compounds of formula I were determined in the following way. Compounds were tested initially at a particular dose level, for example 90 mg/kg. If the compound was considered sufficiently active (giving a reduction of blood pressure equal to or greater than 16% after

correction) it was retested at a lower dose level, for example 30 mg/kg. By testing at successively lower dose levels, a threshold antihypertensive dose (dose giving a reduction of blood pressure of between 9 and 16% after correction) was determined. Compounds inactive at a particular dose level and giving a reduction of blood pressure equal to or greater than 16% after correction at the next highest dose level were designated as having a threshold antihypertensive dose within the range covered by the two dose levels.

The final products of Examples 1 to 7 were active in this test at a dose level of 90 mg/kg or less and the actual results obtained are shown in Table 1 below.

Table 1

Final Product of Example	Threshold antihypertensive dose (mg/kg)
1	3-10
2	3
3	3
4	3-10
5	10-30
6	30-90
7	30-90

The invention is illustrated by the following non-limitative Examples in which compositions of mixed solvents are given by volume. Novel compounds were

characterised by one or more of the following: elemental analysis, nuclear magnetic resonance and infra-red spectroscopy. Temperatures are given in degrees Celsius.

Flash chromatography was performed according to the method of Still et al., J. Org. Chem., 43, 2923-5 (1978).

Example 1

(a) Water (80 ml) was added to a stirred mixture of 3-trifluoromethoxyaniline (10 g) and concentrated hydrochloric acid (5 ml) at ambient temperature. The resultant solution was cooled to 0° and a solution of methyl 3-hydroxy-2-(methylthio)acrylate, sodium salt (80 mole %, 11.5 g) in water (60 ml) added over 20 minutes. The mixture was stirred whilst allowing to warm to ambient temperature and then stirred for 4 hours. The solid was collected by filtration and washed with water (2 x 100 ml) to give methyl 2-methylthio-3-(3-trifluoromethoxyanilino)acrylate, m.p. 58-61°.

(b) Methyl 2-methylthio-3-(3-trifluoromethoxyanilino)-acrylate (16.5 g) was added portionwise over 15 minutes to boiling diphenyl ether (300 ml) stirred under nitrogen. After stirring at approximately 260° for 30 minutes, the mixture was allowed to cool to ambient temperature and diethyl ether (600 ml) added with stirring. The solid was collected by filtration and washed with diethyl ether (100 ml) to give 4-hydroxy-3-methylthio-7-trifluoromethoxyquinoline, m.p. 270° (dec.).

(c) Dimethyl sulphate (4.5 ml) was added to a stirred solution of 4-hydroxy-3-methylthio-7-trifluoromethoxy-quinoline (7 g) and potassium hydroxide (2.85 g) in tetrahydrofuran (15 ml) and water (55 ml) at ambient temperature and the mixture stirred for 5 hours. The solid was collected by filtration and washed with water (2 x 50 ml) to give 1-methyl-3-methylthio-7-trifluoromethoxy-4-quinolone, m.p. 130°.

Example 2

(a) Water (125 ml) was added to a stirred mixture of 3-trifluoromethylthioaniline (17.8 g) and concentrated hydrochloric acid (8.5 ml) and the mixture stirred at 40° for 5 minutes. The resultant solution was cooled to 0° and a solution of methyl 3-hydroxy-2-(methylthio)acrylate, sodium salt (80 mole %, 19.55 g) in water (100 ml) added over 30 minutes. After stirring at ambient temperature for 3 hours the mixture was kept overnight. The mixture was extracted with dichloromethane (3 x 200 ml) and the combined extracts washed with aqueous hydrochloric acid (5M, 75 ml) then water (200 ml). The extract was dried over magnesium sulphate and the solvent removed by evaporation to give methyl 2-methylthio-3-(3-trifluoromethylthioanilino)-acrylate as an oil.

(b) A solution of methyl 2-methylthio-3-(3-trifluoromethylthioanilino)acrylate (26.8g) in warm (30-40°) diphenyl ether (50 ml) was added dropwise over 15 to 20 minutes to boiling diphenyl ether (100 ml) stirred under nitrogen. After stirring at approximately 260° for 25 minutes the mixture was allowed to cool to ambient temperature and diethyl ether (300 ml) added with stirring. The solid was collected by filtration and washed with diethyl ether (100 ml) to give a mixture of 4-hydroxy-3-methylthio-5-trifluoromethylthioquinoline and 4-hydroxy-3-methylthio-7-trifluoromethylthioquinoline, m.p. 222-224°.

(c) Dimethyl sulphate (5.2 ml) was added to a stirred solution of the isomeric mixture of 5- and 7-trifluoromethylthio-4-hydroxy-3-methylthioquinolines (14.55 g) and potassium hydroxide (3.1 g) in tetrahydrofuran (150 ml) and water (200 ml) at ambient temperature. After stirring for 6 hours the mixture was kept

overnight. The solid was collected by filtration, washed with water (2 x 100 ml) and crystallised from industrial methylated spirit (250 ml) to give a mixture of 1-methyl-3-methylthio-5-trifluoromethylthio-4-quinolone and 1-methyl-3-methylthio-7-trifluoromethylthio-4-quinolone. The mixture was dissolved in dichloromethane and separated by high pressure liquid chromatography on a silica gel column eluted with dichloromethane to give 1-methyl-3-methylthio-7-trifluoromethylthio-4-quinolone, m.p. 168-172°.

Example 3

A solution of 3-chloroperoxybenzoic acid (85% w/w, 2.68 g) in dichloromethane (50 ml) was added dropwise over 30 minutes to a stirred solution of 1-methyl-3-methylthio-7-trifluoromethoxy-4-quinolone (4.5 g), prepared as described in Example 1, in dichloromethane (100 ml) at 0-5°. The mixture was allowed to warm to ambient temperature and stirring continued for 2.5 hours. 3-Chloroperoxybenzoic acid (85% w/w, 0.2 g) in dichloromethane (5 ml) was added and the mixture was stirred for 2 hours, then allowed to stand for 2 days. Further 3-chloroperoxybenzoic acid (85% w/w, 0.11 g) was added and the mixture stirred for 4 hours. The mixture was washed with saturated aqueous sodium bicarbonate (2 x 100 ml) then water (100 ml) and the organic phase dried over magnesium sulphate. The solvent was removed by evaporation and the residue crystallised from ethyl acetate (250 ml) to give 1-methyl-3-methylsulphinyl-7-trifluoromethoxy-4-quinolone, m.p. 200-201°.

Example 4

A solution of 3-chloroperoxybenzoic acid (55% w/w, 0.668 g) in dichloromethane (25 ml) was added

dropwise over 2 hours to a stirred solution of 1-methyl-3-methylthio-7-trifluoromethylthio-4-quinolone (0.65 g), prepared as described in Example 2, in dichloromethane (80 ml) at -20°. The mixture was allowed to warm to ambient temperature, then washed with saturated aqueous sodium bicarbonate (2 x 25 ml) followed by water (35 ml) and the organic phase dried over magnesium sulphate. The solvent was removed by evaporation and the residue purified by flash column chromatography on a silica gel column eluted with dichloromethane:industrial methylated spirit (9:1) to give 1-methyl-3-methylsulphinyl-7-trifluoromethylthio-4-quinolone, m.p. 238-239°.

Example 5

A solution of 3-chloroperoxybenzoic acid (85% w/w, 0.4 g) in dichloromethane (5 ml) was added to a stirred solution of 1-methyl-3-methylsulphinyl-7-trifluoromethoxy-4-quinolone (0.63 g), prepared as described in Example 3, in dichloromethane (25 ml) at ambient temperature. The mixture was stirred for 3 hours, then washed with saturated aqueous sodium bicarbonate (15 ml) followed by water (20 ml) and the organic phase dried over magnesium sulphate. The solvent was removed by evaporation and the residue crystallised from industrial methylated spirit (10 ml) to give 1-methyl-3-methylsulphonyl-7-trifluoromethoxy-4-quinolone, m.p. 249-250°.

Example 6

a) Chlorodifluoromethane was passed into a stirred solution of 7-hydroxy-1-methyl-3-methylthio-4-quinolone (3.4 g), prepared as described in UK Patent No.2047691, and sodium hydroxide (3.0 g) in a mixture of dioxan (10 ml) and water (8 ml) at 90°. Further

dioxan (5 ml) and water (4 ml) were added. Chlorodifluoromethane was passed into the mixture at 90° for a further 20 minutes. The reaction mixture was cooled to ambient temperature, the solid collected by filtration and washed with water (4 x 10 ml) to give 7-difluoromethoxy-1-methyl-3-methylthio-4-quinolone, m.p. 152-159°.

b) A solution of 3-chloroperoxybenzoic acid (85% w/w, 0.33 g) in chloroform (25 ml) was added dropwise to a stirred solution of 7-difluoromethoxy-1-methyl-3-methylthio-4-quinolone (0.54 g) in chloroform (25 ml) at -5°. The mixture was stirred at -5° for 1 hour, poured into saturated aqueous sodium bicarbonate (200 ml) and the layers separated. The aqueous layer was extracted with chloroform (2 x 100 ml). The original chloroform layer and extracts were combined and dried over magnesium sulphate. The solvent was removed by evaporation and the residue crystallised from ethyl acetate to give 7-difluoromethoxy-1-methyl-3-methylsulphinyl-4-quinolone, m.p. 198-200°.

Example 7

Sodium (0.45 g) was added portionwise to a stirred mixture of 2,2,2-trifluoroethanol (3 ml) and dry dioxan (30 ml). 7-Fluoro-1-methyl-3-methylsulphinyl-4-quinolone (4.5 g), prepared as described in UK Patent No. 2047691, was added to the resultant solution and the mixture stirred at 95-100° for 24 hours. The reaction mixture was cooled to ambient temperature and the solid was collected by filtration and crystallised from industrial methylated spirit (50 ml) to give 1-methyl-3-methylsulphinyl-7-(2,2,2-trifluoroethoxy)-4-quinolone, m.p. 288-291°.

Example 8

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing 10 mg of active compound.

Example 9

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinylpyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets containing 10 mg of active compound.

Example 10

Tablets are prepared by the method of Example 9. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

Example 11

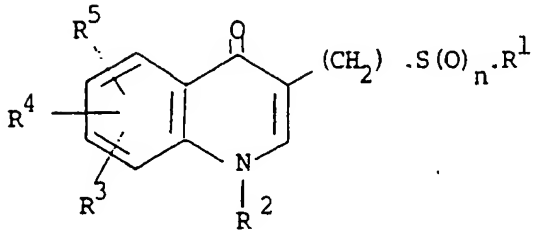
In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of semi-synthetic glycerides as the suppository base and the mixture formed into suppositories each containing 100 mg of active ingredient.

Example 12

In the preparation of capsules, 50 parts by weight of active compound, 300 parts by weight of lactose and 3 parts by weight of magnesium stearate are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing 50 mg of active compound.

Claims

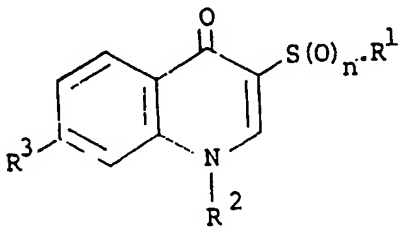
1. A compound of formula I



I

in which R^1 is lower alkyl; R^2 is lower alkyl; R^3 is halogenated lower alkoxy, halogenated lower alkylthio, halogenated lower alkylsulphinyl or halogenated lower alkylsulphonyl; R^4 and R^5, which may be the same or different, are hydrogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulphinyl, lower alkylsulphonyl, halo, halogenated lower alkyl, halogenated lower alkoxy, halogenated lower alkylthio, halogenated lower alkylsulphinyl, halogenated lower alkylsulphonyl, cyano, phenyl or phenyl substituted by 1 to 3, especially 1 or 2, groups selected from lower alkyl, lower alkoxy, halo or halogenated lower alkyl; m is 0 or 1; and n is 0, 1 or 2.

2. A compound as claimed in claim 1 represented by formula II



II

in which R^1 is lower alkyl; R^2 is lower alkyl; R^3 is halogenated lower alkoxy, halogenated lower alkylthio,

halogenated lower alkylsulphinyl or halogenated lower alkylsulphonyl; and n is 0, 1 or 2.

3. A compound as claimed in claim 2 in which R^1 is alkyl having 1 to 4 carbon atoms; R^2 is alkyl having 1 to 4 carbon atoms; R^3 is fluorinated alkoxy having 1 to 4 carbon atoms, fluorinated alkylthio having 1 to 4 carbon atoms, fluorinated alkylsulphinyl having 1 to 4 carbon atoms or fluorinated alkylsulphonyl having 1 to 4 carbon atoms; and n is 0, 1 or 2.

4. A compound as claimed in claim 3 in which R^3 is trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy or trifluoromethylthio.

5. A compound as claimed in claim 4 in which R^1 and R^2 are methyl.

6. 1-Methyl-3-methylthio-7-trifluoromethoxy-4-quinolone.

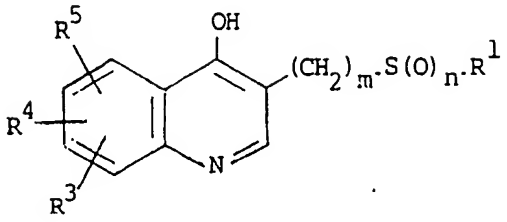
7. A pharmaceutical composition which comprises a compound of formula I as claimed in any one of claims 1 to 6 together with a pharmaceutically acceptable carrier.

8. A method of treating hypertension in a mammal in need of such treatment which comprises the administration of a compound of formula I as claimed in any one of claims 1 to 6.

9. A compound of formula I as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment of hypertension.

10. A process for the preparation of compounds of formula I as claimed in claim 1 which comprises

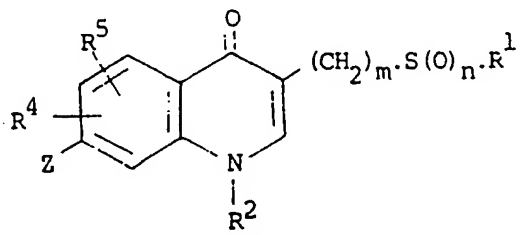
(a) alkylation of a compound of formula III



III

with an alkylating agent of formula $(R^2)_2SO_4$ or an alkylating agent of formula R^2Y in which Y is a leaving group;

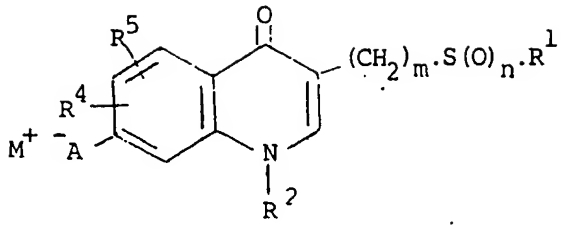
(b) to prepare compounds of formula I in which R^3 is halogenated lower alkoxy, halogenated lower alkylthio or halogenated lower alkylsulphonyl in the 7-position of the quinoline ring, reaction of a compound of formula VII



VII

in which Z is fluoro, chloro or bromo, with the appropriate halogenated anion in a solvent inert to the conditions of the reaction; or

(c) to prepare compounds of formula I in which R^3 is halogenated lower alkoxy or halogenated lower alkylthio in the 7-position of the quinoline ring, reaction of a compound of formula VIII



VIII

in which A is oxygen or sulphur and M^+ is a cation, with an appropriate alkylating agent.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001376 SA 39413

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/12/90
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